## REMARKS

Status of the Claims

Claims 1-24, and 27-44 are now pending in the present application. Claims 1, 8, 16, 27, and 29-43 have been amended to more clearly define over the art cited, and new Claim 44 has been added. Claims 25 and 26 were canceled in a previous response.

Election/Restrictions

The Examiner has indicated that Restriction to one of the two groups of Claims is required under 35 U.S.C. 121, since the claims are drawn to two patentably distinct groups, where a Group I includes Claims 1-24, drawn to identifying a cell based on spatial frequency from image data, classified in Class 382, subclass 133, as well as Claims 27-28, drawn to using a nuclear marker to identify a cell, classified in Class 382, subclass 133, and a Group II which includes Claims 29-43, drawn to determining a viability status of an identified cell based on a collection of images from different sensing systems – specifically darkfield, brightfield, and fluorescent, classified in Class 382, subclass 181. The Examiner indicates that the inventions in Groups I and II are related as subcombinations disclosed as usable together in a single combination, and that each subcombination has separate utility. Further, the Examiner notes that since applicants have received an action on the merits for the claims of Group I, the invention of Group I (i.e., Claims 1-24 and Claims 27-28) have been constructively elected by their original presentation for prosecution on the merits.

While applicants are not traversing the Restriction as applied to Claims 29-43 as previously presented, applicants have amended each of Claims 29-43 and added new Claim 44, so that all of the claims are now within the subject matter recited in the claims included in Group I and are no longer directed to subject matter that is in a different Class and subclass.

Applicants emphasize that the recitation of independent Claims 1, 8, and 16 is directed to much of the same subject matter recited in Claims 29-44 as now amended. For example, Claim 8 provides for obtaining "the brightfield image of the specific cell," while Claim 16 provides for "contacting the specific cell with the nuclear marker." Dependent Claims 5 and 6, and Claims 20 and 21 provide for determining if a specific cell is an early or late stage apoptotic, or a necrotic cell type. Accordingly, the Examiner will NOT be required to do any additional searching to consider the patentability of Claims 29-44 as now amended, since the ***amended*** claims are properly included within the claims of Group I. For this reason,



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the applicants request the Examiner to examine Claims 29-44 in the present application. The patentability of these claims is discussed below.

Claims Rejected under 35 U.S.C. 102(b)

The Examiner has rejected Claims 27 and 28 under 35 U.S.C. § 102(b) as being anticipated by U.S. Pub. Application No. 2002/0159625 (Elling). The Examiner notes that Elling discloses a kit and uses a single stain to identify "living and fixed (death) cells", which corresponds to the recitation in Claim 27 of contacting a cell "with the single nuclear marker for a time sufficient to allow identification of an apoptotic cell or a necrotic cell with the multispectral imaging system using only a single nuclear marker."

Applicants respectfully disagree with the Examiner's interpretation of the teaching in Elling and his conclusion that Elling teaches what applicants have recited in Claim 27. For example, Elling does not teach or suggest the use of a single nuclear marker to identify whether a cell is an apoptotic cell or a necrotic cell. Indeed, Elling does not refer to either an apoptotic cell or a necrotic cell. A "fixed cell" is a cell that has been treated to accept a stain, and as a result of the fixation, is a dead cell, as the Examiner indicates. Many stains are ineffective on living cells, and require that a cell be fixed to enable the stain to penetrate the cell membrane. However, the use of a stain on either living or fixed (i.e., dead) cells does not imply that the cells are being stained and imaged to identify a cell as either apoptotic or necrotic. Also, cells that are dead are not necessarily fixed with a fixative to facilitate staining. Further, a dead or dying cell can be either apoptotic or necrotic and may not be either because the cell is fixed.

While in paragraph [0076], Elling lists a number of reagents that "are used to label the nucleus of living and fixed cells," Elling does not teach or suggest that any of these reagents are used to produce images for the purpose of identifying a cell as an apoptotic cell or as a necrotic cell. Paragraph [0004] in applicants' application as published provides a discussion of the clear differences between apoptotic cell death and cell necrosis. There is no teaching or suggestion in Elling of making an identification of a cell as being of either of these two types of cells. Instead, Elling simply indicates that the listed reagents can be applied to both living cells and fixed cells, but does not teach or suggest how an image of a cell that has contacted a single nuclear marker can be used to determine if the cell is either an apoptotic cell or a necrotic cell. The fact that one of the reagents listed by Elling is the same as recited in Claim 28 is not determinative of Elling teaching that function, since reagents can be used to label a cell nucleus for a number of different purposes not related to identifying a cell as apoptotic or necrotic, and Elling does not



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teach or suggest the use of 7-aminoactinomycin D for use in identifying a cell as an apoptotic cell or a necrotic cell. Accordingly, Claims 27-28 are both novel and non-obvious over the art cited.

Claims Rejected under 35 U.S.C. § 103(a)

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 6,211,955 (Basiji et al.- hereinafter "Basiji") in view of U.S. Patent No. 6,671,624 (Dunlay). The Examiner acknowledges that Basiji does not teach determining whether a specific cell corresponds to a known cell type by comparing a spatial frequency content of a side scatter image of a known cell type to the spatial frequency content data of a side scatter image of the specific cell. The Examiner states that Dunlay "performs the comparison of morphology features selected from the database in order to identify whether those specific cells are in the image and collect data only on those specific cells." Applicants have amended Claim 1 to clearly indicate that "***the known cell type relates to the viability of the cell***." Accordingly, applicants respectfully disagree that Dunlay teaches or suggests any type of comparison of spatial frequency data for side scatter image data (or any data) for a known type of cell with data for an unknown type of cell – particularly where the known type of cell relates to the viability of the cell. The Examiner has cited to Fig. 9 in Dunlay and to Col. 14, but there is no mention or suggestion of comparing ***any type of data*** for a known type of cell ***of any type*** with that of an unknown cell in either Fig. 9, or in any other portion of Dunlay. Accordingly, there is no justification for the Examiner to assert that it would be obvious to modify Basiji to enable such a comparison to be made because of any teaching in Dunlay. Instead, Dunlay enables a user to make a "selection of various parameter settings used to identify nuclei and cytoplasm, and selection of different fluorescent reagents, identification of cells of interest based on morphology or brightness, and cell numbers to be analyzed per well." Dunlay uses the parameter settings to identify cells of interest based on form and structure (i.e., morphology), or brightness. Dunlay makes an absolute identification using the parameters and the indicia of the cell type – but does not make an identification that is based on a comparison of the spatial frequency content of a known type of cell with that of the specific cell for a type of cell relating to the viability of the cell. Thus, this rejection should be withdrawn.

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as unpatentable over Basiji in view of U.S. Published Application No. 2004/0093166 (Kil). The Examiner relies upon Kil for teaching "the identification of cells by comparing extracted features (including morphology, texture information (spatial frequency)) to a unknown cell to identify the cell of interest, and further classify the cell as a known



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type," with reference to Fig. 5, and paragraphs [0060], [0098], and [0103] of Kil. The Examiner asserts that it would have been obvious "to modify the method of Kil, by performing a comparison operation of previous acquired features (morphological/spatial frequency) and use these features in identifying a specific cell in the image acquired by Basiji according to the teaching of Kil." Applicants respectfully disagree with this assertion. The Examiner is asserting that it would be obvious to ***modify the teaching of Kil*** to carry out applicants' step of "comparing the spatial frequency content of the side scatter image of the specific cell to the spatial frequency content data of the side scatter image of the known cell type to determine if the specific cell corresponds to the known cell type," ***and further, that it would then be obvious to modify the teaching of Basiji to use the features of Kil as thus modified***. The Examiner is not permitted to reject a claim based on modifying a first reference in a manner that is not taught or suggested by any cited art, and then modifying a second reference to use the modified first reference. In this case, there is no teaching in Kil about determining if a specific cell corresponds to a known cell type, where the cell type is in regard to the viability of the cell, by comparing the spatial frequency content of a side scatter image for a known type of cell with that of a specific cell. Instead, Kil relies on "variable abstraction processing" or pixel processing using various spectral attributes such as RBG values of pixels, to determine a region of interest (ROI), as explained in paragraph [0060]. At paragraph [0098], Kil teaches that a data image file produced by the pixel processing is loaded and then, sub image processing is carried out so that either a new sub image processing database is created if the user doesn't want to use an existing database or the existing sub image database is classified. Paragraph [0103] of Kil explains how feature extraction is applied to the sub image database during a run sub image classification procedure and lists the various features that can be extracted. Nothing in the reference suggests or implies that any procedure in Kil involves a comparison of the spatial frequency content of a side scatter image for a known type of cell with that of a specific cell. Accordingly, there is no reason why one of ordinary skill in the art would be led by the teaching of Basiji and Kil to implement applicants' method as recited in these claims.

Claims 1-3 are further rejected as unpatentable over Basiji in view of U.S. Patent No. 7,042,639 (McDowell et al. – hereinafter "McDowell"). Again acknowledging that Basiji does not teach any comparison of the spatial frequency content of side scatter images to determine a type of a specific cell, where the type of cell is in regard to the viability of the cell, the Examiner relies on McDowell for teaching "the identification of a specific cell by comparing produced metrics against known metrics to



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identify and classify cells," with reference to Fig. 19A and Cols. 12, 13, and 14. The Examiner then concludes that it would be obvious "to modify the method of Basiji, by performing a comparison operation of previous acquired features (morphology/spatial frequency) and use these features in identifying a specific cell in the image acquired by Basiji according to the teaching and motivation set forth in McDowell." Applicants again respectfully disagree.

It should be noted that Fig. 19A and the corresponding text in Cols. 12-14 of McDowell are directed to determining if a cell is a "good" or "bad" candidate for use in patch clamping. McDowell discloses techniques that are not used for determining a type of specific cell, particularly where the cell type is in regard to a viability of the cell. Instead, McDowell discloses an automated approach for processing video digital image frames obtained with a microscope. The example described by McDowell in connection with Fig. 19A is intended to illustrate how an object such as a cell can be distinguished relative to a background, and how metrics such as "intensity weighted center of mass (centroid), major axis length, minor axis length, area, roundness, smoothness, elongation, shape, partial cells, and cell orientation" (bottom of Col. 12) can be used to identify a good candidate cell for patch clamping. McDowell does not teach or suggest the use of spatial frequency content data in a side scatter image for determining a type of a specific cell, where the type of cell is in regard to cell viability, by comparison of the spatial frequency content data of a known type of cell to that of a specific cell. Instead, McDowell uses a neural network to evaluate the metrics automatically determined for a cell to classify the cell as good or bad for patch clamping, by first isolating cells from the background in an image. The non-background objects are then analyzed to produce a matrix of the specimen being held in the holder, as shown in Table 2 at the bottom of Col. 14 and top of Col. 15. McDowell then indicates (Col. 15) that the program "compares the produced metrics of Table 2 against known metrics to identify and classify the one or more cells being held in the holder 14." The metrics of McDowell are not equivalent to spatial frequency content data for images of a known type and a specific cell. Further, the McDowell reference teaches that an ideal patch clamping candidate is classified by its "major axis, minor axis, area, elongation, roundness, smoothness, theta (orientation with respect to a coordinate system), thinness, and whether the object is completely (F) contained in the field of view or only partially contained (partial)." These are the metrics used by the neural network to determine whether a cell in a holder of the microscope is a good patch clamping candidate – not spatial frequency data. The only comparison is between the metrics of cells in the holder against the metrics known to be appropriate for a good patch



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clamp candidate cell. Further, McDowell does not teach or suggest that such metrics have any utility in determining a type of cell in regard to the viability of the cell. One of ordinary skill in the art would therefore not have been led to modify Basiji to compare the spatial frequency data of a known type of cell with that of a specific cell to determine the type of cell in regard to cell viability. The teaching of McDowell is simply too disparate from the concept recited in Claim 1 to logically arrive at the conclusion that applicants' recited steps would be obvious to one of ordinary skill in the art, based on modifying Basiji as taught by McDowell. This rejection should therefore be withdrawn.

Claims 1-3 are still further rejected as unpatentable over Basiji in view of U.S. Patent No. 5,828,776 (Lee et al. – hereinafter "Lee"). The Examiner again notes that Basiji is silent in regard to "determining whether a specific cell corresponds to a known cell type" by comparing the spatial frequency content data from a side scatter image of the known cell type to that of the specific cell – particularly where the cell type is in regard to cell viability. The Examiner notes that Lee teaches processing a biological specimen such as a Pap smear on a slide to generate an analysis score that is indicative of whether the specimen is cancerous. The approach described by Lee in Fig. 29 includes the steps of: building a feature library; acquiring equal numbers of abnormal groups of cells and cellular and non-cellular artifacts; computing features on new objects; selecting features that best discriminate between abnormal groups and cellular and non-cellular artifacts; and building a classifier or box filter for those objects. The system includes: a single cell classifier; a group classifier; a thick group classifier; and an FOV integrator. The potential pre-malignant or malignant cells in a field of view (FOV) of the image are identified and assigned a confidence value for each detected object. Further confidence in the classification of single cells is obtained by use of the other two classifiers, since if all three classifiers indicate abnormal cells are present, the result is more likely accurate. However, Lee notes that inconsistent results for the three classifiers can be obtained and must be further resolved. Further, the FOV results of multiple classifiers are correlated and accumulated to improve the slide classification results. The FOV correlation features are relatively specific and comprise a rather long list provided in Col. 8 of the reference. In reviewing these features, it is apparent that Lee is not comparing the spatial frequency content of images for a cell of a known type with that of a specific cell, to determine the type of cell in regard to the viability of the cell. The identification of a normal or abnormal (cancerous) cell does not relate to the viability of the cell, since both normal and cancerous cells are viable. Accordingly, the



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teaching of Lee is not useful for modifying Basiji, as suggested by the Examiner, and Claims 1-3 are not obvious over this combination of references.

Claims 8, 9, 10, and 15-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Published Application No. 2002/0071121 (Ortyn et al. – hereinafter "Ortyn") in view of McDowell. In regard to independent Claim 8, the Examiner indicates that Ortyn teaches using a brightfield image to more accurately analyze morphological detail, where morphological parameters include spatial frequency content, but acknowledges that Ortyn is silent in regard to determining whether a specific cell corresponds to a known cell type, and in regard to independent Claim 16, that Ortyn does not teach providing an image of a known cell type that has been marked with a nuclear marker or providing spatial frequency content data from the image of the cell of the known type, and in regard to both claims, Ortyn does not teach "comparing the spatial frequency content of the brightfield image of the specific cell to the spatial frequency content data of the brightfield image of the known cell type." The Examiner asserts that it would have been obvious to one of ordinary skill in the art to modify the method of Ortyn by performing a comparison of acquired features (spatial frequency) for use in identifying a specific cell in the image according the method of using the metrics as taught by McDowell. Applicants respectfully disagree.

As noted above, the metrics disclosed by McDowell for a determination such as whether a cell is a good or bad candidate for patch clamping are not related to spatial frequency content. Further, neither McDowell nor Ortyn teach or suggest how the spatial frequency content of a brightfield image of a specific cell can be compared to the spatial frequency content data of the brightfield image of a known cell type to determine if the specific cell corresponds to the known cell type (in Claim 8), comparing the image of the marked specific cell and a spatial frequency content of the image of the marked specific cell to the marked image of the known cell and the spatial frequency content of the marked image of the known cell type to determine if the specific cell corresponds to the known cell type (in Claim 16) – particularly where the known cell type relates to the viability of the cell (both Claims 8 and 16). McDowell does not provide sufficient details of any equivalent comparison, since the metrics taught by McDowell are not related to the spatial content data from a brightfield image or the marked image and spatial frequency content of the marked image used in the Claims 8 and 16, respectively, to justify the assertion made by the Examiner in rejecting these claims, and the rejection should be withdrawn.

Claims 16, 17, 18, and 23 are rejected as unpatentable over U.S. Published Application No. 2003/0059093 (Rosania et al. – hereinafter "Rosania") in view of McDowell. In regard to Claim 16,



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the Examiner asserts that Rosania teaches all of the steps recited in the claim, except determining whether the specific cell "corresponds to a known cell type," or the steps of "providing an image of the known cell type that has been marked with a nuclear marker, providing spatial frequency content data from the image of the known cell type that has been marked with the nuclear marker, [and] comparing the image of the marked specific cell and in combination a spatial frequency content of the image of the marked specific cell to identify a to (*sic*) the marked image of the known cell and the spatial frequency content of the marked image of the known cell type to determine the specific cell corresponds to the known cell type." The Examiner relies on McDowell for teaching "the identification of a specific cell by comparing produced metrics against known metrics to identify and classify cells as displayed in Fig. 19A and described in detail in Cols. 12, 13." The Examiner concludes that it would have been obvious to modify the method of Rosania, by performing a comparison operation of previous acquired features in identifying a specific cell in an image acquired as taught by Rosania. Applicants again respectfully disagree.

The first sentence in paragraph [0024] of Rosania indicates that the intended function of the cited reference is "automated methods for determining the organization of a cellular component of interest in individual cells as a function of its position relative to a cellular reference component." Rosania teaches the use of an optically detected reporter molecule to carry out that intended function (see paragraph [0029]). As the Examiner noted, at paragraph [0057], Rosania also teaches the use of a "Fourier transform analysis to determine the spatial frequency of the signals from the cellular component reporter molecule(s)," and at paragraph [0059], the reference teaches the use of the Fourier transform function describing the distribution of pixel intensities within and/or between the domains." However, Rosania does NOT teach or suggest "providing an image of the known cell type that has been marked with a nuclear marker," as recited in applicants' claim, and does NOT teach or suggest "providing spatial frequency content data from the image of the known cell type that has been marked with the nuclear marker." There is no indication in Rosania of using a "known cell type" for any purpose, which is not surprising, since Rosania is attempting to determine the organization of a cellular component of interest – which does not require the use of a known cell type for any purpose. Further to what was discussed above, McDowell does not teach a comparison of the image of a marked specific cell and a spatial frequency content of the image of the marked specific cell to a marked image of a known cell and the spatial frequency content of the marked image of the known cell type to determine if the specific cell corresponds to the known cell type. McDowell discloses automated techniques for determining if a cell is



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a good or bad candidate for a particular application and does not use spatial frequency content of a marked image of a known type of cell. Accordingly, there is no reason why one of ordinary skill in the art would be led to produce what applicants recite in Claim 16 and the rejection of this claim should be withdrawn.

Claims 4 and 7 have been rejected as unpatentable over Basiji and McDowell as applied above, and further in view of U.S. Published Application No. 2003/0040031 (Kim). The Examiner asserts that Kim teaches cell analysis of cell images to identify cells that are dead and then extends that assertion to indicate that it would be obvious to modify Basiji as modified by McDowell to identify an apoptotic cell. However, Kim does not teach or suggest identifying an apoptotic cell. Instead Kim only teaches "cell death," as indicated in the last line of paragraph [0227], but does not teach or suggest that an apoptotic cell is identified, for example, in contrast to a necrotic cell. The Examiner is cautioned that the more general reference to "cell death" does not provide any basis for asserting that Kim identifies an apoptotic cell, since the two terms are NOT synonymous. As noted above, applicants have described the meaning of apoptotic and necrotic in the Background portion of their specification, and there is no teaching or suggestion in Kim of identifying an apoptotic cell as described by applicants (and as known in the art).

Claims 11 and 14 are rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ortyn and McDowell as applied above, and further in view of Kim.

Claims 19 and 22 are rejected under 35 U.S.C. § 103(a) as unpatentable over Rosania and McDowell, as applied above, and further in view of Kim.

In the interest of reducing the complexity of the issues for the Examiner to consider in this response, the discussion presented above focuses on independent Claims 1, 8, 16, and 27. The patentability of each remaining dependent claim is not necessarily separately addressed in detail. However, applicants' decision not to discuss the differences between the cited art and each dependent claim should not be considered as an admission that applicants concur with the Examiner's conclusion that these dependent claims are not patentable over the disclosure in the cited references. Similarly, applicants' decision not to discuss differences between the prior art and every claim element, or every comment made by the Examiner, should not be considered as an admission that applicants concur with the Examiner's interpretation and assertions regarding those claims. Indeed, applicants believe that all of the dependent claims patentably distinguish over the references cited. In any event, a specific traverse of



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the rejection of each dependent claim is not required, since dependent claims are patentable for at least the same reasons as the independent claims from which the dependent claims ultimately depend.

Patentability of Independent Claim 29

As noted above, applicants have amended Claims 29-43 so that they are now within Group I and have added new Claim 44. Independent Claim 29 (as now amended) recites the following:

> 29. A method for identifying a specific cell, to determine a type of the specific cell, comprising the steps of:
>
> exposing the specific cell to a nuclear marker that will bind to DNA in a nucleus of the cell;
>
> collecting spatial frequency image data of the specific cell in which the nuclear marker is present; and
>
> analyzing the spatial frequency image data to determine a type of the specific cell, wherein the type of the specific cell is determined by a condition of material in the nucleus of the specific cell, as indicated by the spatial frequency image data.

None of the art cited teaches or suggests analyzing spatial frequency image data for a cell in which a nuclear marker is bound to DNA in the nucleus of the specific cell, to determine a type of the specific cell, where the type is determined by a condition of the material in the nucleus of the specific cell indicated by the spatial frequency image data. Accordingly, Claim 29 is patentable over the art of record.

Because dependent claims inherently include each element recited in the independent claim upon which they ultimately depend, each claim depending upon independent Claim 29 is patentable for at least the same reasons as those discussed above.

In consideration of the amendment to the claims and the Remarks set forth above, it is applicants' position that all claims in the current application are patentable over the art of record. The Examiner is thus requested to pass this case to issue without further delay. In the event that any other issues remain, the Examiner is invited to telephone applicants' attorney at the number listed below.

Respectfully submitted,

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